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## **Concise Synthesis of Taxol A-Ring Components: Remote Diastereoselective Additions of Alkenyl Lithiums to Aldehydes**

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Abstract: The acid chloride 6 provides access to 7 (R,S and S,S) which upon bromine-lithium exchange undergoes remarkably highly diastereoselective additions to aldehydes; 7 is also readily elaborated into the acetal 10. Copyright © 1996 Elsevier Science Ltd



One of the most direct and convergent approaches to the synthesis of the highly functionalized taxol core structure<sup>1</sup> is depicted in **Scheme 1**.<sup>2</sup> Construction of the A-ring component and the C-ring unit allows for a multitude of ways to subsequently link them together, one of which is the union of **2** and

 $3.^3$  To explore this, and other options, we required a short route to the A-ring 2 (or equivalent) in an enantiomerically enriched form. While there have been many reports describing the synthesis of the taxol A-ring in various oxidation levels,<sup>4</sup> the chemistry described here uncovered some new observations which are useful for the specific case of taxol, but also should be valuable in the broader arena of synthesis.



Tetramethylethylene was converted into the *gem*-dibromocyclopropane 4, which on treatment with PhNMe<sub>2</sub> at 148°C gave the bromodiene 5, Scheme 2.<sup>5</sup> This modification of the literature procedure more than doubles the yield of 5 and is amenable to large scale (100 g). The diene 5 reacted cleanly with acryloyl chloride in a thermal (110°C) Diels-Alder process to give 6 (95%), with no more than traces of the other regioisomer

(<5%). All attempts to catalyze this reaction with chiral Lewis acids, or chiral derivatives of acryloyl chloride were unsuccessful.<sup>6</sup> Consequently, **6** was treated with S-(-)-PhCHMeNH<sub>2</sub> to give a 1:1 mixture of **7** (R,S) and **7** (S,S) which were readily separable, and the absolute stereochemistry of one of the diastereomers determined by X-ray crystallography. Figure 1 show a Chem 3D representation from the x-ray coordinates of the **7** (S,S) diastereomer, and therefore the other diastereomer **7** (R,S) corresponds to the correct absolute configuration needed for the synthesis of taxol.

Since the *sec*-amide formation to give 7 had accomplished the resolution of the A-ring we decided to examine halogen-metal exchange on this derivative rather than the traditional esters, **Scheme 3**.



Conditions:-a) CrO3/3,5-DMP/CH<sub>2</sub>Cl<sub>2</sub>/-15°C **8** (76%). b) i. N<sub>2</sub>O<sub>4</sub>/CCl<sub>4</sub>/CHCl<sub>3</sub>/-40 to 0°C (96%). ii. 0.1 M NaOH/80°C (66%). iii. Mel/acetone/K<sub>2</sub>CO<sub>3</sub> (89%). iv. NaBH<sub>4</sub>/MeOH/-15°C (91%). v. K<sub>2</sub>CO<sub>3</sub>/PhCl/135°C **9** (76%). c) DIBAL-H/CH<sub>2</sub>Cl<sub>2</sub>/-78°C, followed by (MeO)<sub>3</sub>CH/MeOH/CSA **10** (68%). d) *t*-BuLi/Et<sub>2</sub>O/-78°C, followed by PhCHO **11** (80%, 3:2). e) *t*-BuLi (6 eq.)/Et<sub>2</sub>O/-78°C/3 h. f) RCHO (10 eq.)/-78°C/Et<sub>2</sub>O, **12/13**.

Treatment of 7 (TABLE 1) with *t*-BuLi (6 equiv. in hexane) gave the dianion 7a which was quenched with an aldehyde to give two diastereomers 12 and 13 (R = Me, Et, Ph and *t*-BuCH<sub>2</sub>). Remarkably, even though the newly created stereogenic center is 7 atoms removed from the chiral benzylic position and 4 atoms from C-1, the observed diastereoselectivity is extraordinarily high. In the case of acetaldehyde (R = Me) the ratio was 20:1, and the structure of the major product was determined by X-ray crystallography, Figure 2.

Substrate	Solvent	Base	Aldehyde	Prodts	Yield %	By-prodt	
7 ( <b>R</b> , <b>R</b> )	Et <sub>2</sub> O	t-BuLi (hex)	MeCHO	20:1	60	Alkene	
7 (R,R)	THF	t-BuLi (hex)	MeCHO	<b>20</b> :1	30	Alkene	
7 (R,R)	Et <sub>2</sub> O	t-BuLi (hex)	EtCHO	15:1	65	Alkene	
7 (R,R)	Et <sub>2</sub> O	t-BuLi (hex)	PhCHO	7:1	50	Alkene	
7 (S,R)	Et <sub>2</sub> O	t-BuLi (hex)	PhCHO	6:1	80	Alkene	
7 (R,R)	Et <sub>2</sub> O	t-BuLi (hex)	t-BuCH <sub>2</sub> CHO	10:1	50	Alkene	
7 (S,R)	Et <sub>2</sub> O	t-BuLi (hex)	t-BuCH <sub>2</sub> CHO	10:1	50	Alkene	

١	Δ	RI	.E.	1

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The only significant by-products were the alkene 7 (Br replaced by H), and small amounts of compounds that were derived from o-metallation of the phenyl ring followed by quenching with the aldehyde. Also, in order to establish that 12 and 13 are diastereomers only at *sec*-OH position and no epimerization at C-1 has taken place, we subjected the mixture of 12 and 13 to the Dess-Martin oxidation conditions to give a single enone.

By way of attempted comparison, the C-1 derivatives -CONMeR\*, -CO<sub>2</sub>Bu<sup>*t*</sup> and -CO-oxazolidinone of **6** did not undergo clean halogen metal exchange, and from the complex mixtures obtained the only discernible product(s) were attack of the *t*-BuLi on the C-1 carbonyl group. The *sec*amide in **7** thus provides a protecting facility for C-1 through the amide anion **7a**.

While it is possible to introduce the C-13 oxygen functionality into very advanced taxol intermediates<sup>7</sup> we were intrigued with the possibility of subjecting **7** to allylic oxidation reactions. A priori, an electrondeficient vinyl bromide might be rather resistant towards this type of transformation, and indeed perusal of the literature did not reveal any pertinent examples other than the oxidation of a vinyl iodide to a  $\beta$ -iodoenone during the course of Kishi's approach to taxol.<sup>8</sup> In the event, treatment of **7** with CrO<sub>3</sub>.3,5-dimethylpyrazole<sup>9</sup> gave the required  $\beta$ -bromoenone **8** (76%).<sup>10</sup> *N*-Nitrosation of **8**, followed by hydrolysis, esterification, reduction and lactonization gave the known lactone **9**.<sup>11</sup> The lactone was reduced with DIBAL-H and the crude lactol treated with CH(OMe)<sub>3</sub>/MeOH/H<sup>+</sup> to give **10**. Bromine-lithium exchange (*t*-BuLi) of **10** and quenching with PhCHO gave **11** (80%) as a 3:2 mixture of diastereomers. Wender has reported that the lactone **9** gave a 3.1:1 ratio of diastereomers (Li, followed by PhCHO).<sup>10</sup> Therefore it appears that the *sec*-amide is the source of the enhanced



diastereoselectivity, presumably through a possible lithium-bridged chelate.<sup>12</sup> It is probable that the dilithio species **7a** is in fact a bridged compound, and the more sophisticated representation in **Scheme 4**, as either a solvated monomer or aggregated species, is a more plausible picture. Reaction of **7a** with acetaldehyde would favor **7b**, which leads to the major diastereomer

12. It would seem unlikely that the cause of the diastereoselectivity is confined only to substrate 7, and we are exploring the notion of long-range lithium chelation (supramolecular) as a more general phenomena to control stereochemistry.<sup>13</sup>

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